

747,772

Set	Items	Description
S1	87	AU='OHARE P' OR AU='OHARE P F J' OR AU='OHARE PJ'
S2	50	AU='NORMAND N' OR AU='NORMAND N M' OR AU='NORMAND N.' OR AU='NORMAND NADIA' OR AU='NORMAND NADIA MICHELLE'
S3	67	AU='BREWIS N' OR AU='BREWIS N D' OR AU='BREWIS N.' OR AU='BREWIS N.D.' OR AU='BREWIS ND' OR AU='BREWIS NEIL' OR AU='BREWIS NEIL D' OR AU='BREWIS NEIL DOUGLAS'
S4	92	AU='PHELAN A' OR AU='PHELAN A.'
S5	10	AU='PHELAN ANN' OR AU='PHELAN ANNE'
S6	286	S1 OR S2 OR S3 OR S4 OR S5
S7	394155	HERPES?
S8	973	VP22
S9	85	VP(W)22
S10	1035	S8 OR S9
S11	791	S7 AND S10
S12	52	S6 AND S11
S13	33	S12 NOT PY>2000
S14	15	RD (unique items)
S15	6323261	CANCER OR TUMOR OR TUMOUR OR NEOPLAS?
S16	296	S11 AND S15
S17	55	S16 NOT PY>1999
S18	39	RD (unique items)
S19	1243856	KINASE
S20	7927	ACF
S21	4188	MULTI (W) DRUG (W) RESISTANC?
S22	164654	ANTISENSE
S23	97192	EXPORT
S24	37	S18 NOT S14
S25	21	S24 AND S19
S26	0	S24 AND S20
S27	0	S24 AND S21
S28	13	S22 AND S24
S29	7	S24 AND S23
S30	2570	S15 AND S21
S31	1	S20 AND S30
S32	2185	S15 AND S20
S33	858	S21/TI
S34	435	S33 AND S30
S35	347	S34 NOT PY>1998
S36	211	RD (unique items)
S37	4213889	REVIEW
S38	23	S36 AND 37
S39	188	S36 NOT S38
S40	631	S20/TI
S41	66	S15 AND S40
S42	41	S41 NOT PY>1998
S43	23	RD (unique items)
?		

14/3,AB/2 (Item 2 from file: 155)
DIALOG(R) File 155:MEDLINE(R)

10553558 20091366 PMID: 10623773

Evaluation of VP22 spread in tissue culture.

Brewis N ; Phelan A ; Webb J; Drew J; Elliott G; O'Hare P

Marie Curie Research Institute, The Chart, Oxted, Surrey RH8 0TL, United Kingdom.

Journal of virology (UNITED STATES) Jan 2000, 74 (2) p1051-6, ISSN 0022-538X Journal Code: 0113724

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

We compare methods of detection of intercellular transport of the **herpes simplex virus protein VP22** and of a green fluorescent protein (GFP)-**VP22** fusion protein. Spread of both proteins was observed by immunofluorescence (IF) using organic fixatives. Spread of both proteins was also detected by IF after paraformaldehyde (PFA) fixation and detergent permeabilization, albeit at reduced levels. However, while spread of GFP-**VP22** was observed by examining intrinsic GFP fluorescence after methanol fixation, little spread was observed after PFA fixation, suggesting that the levels of the fusion protein in recipient cells were below the detection limits of intrinsic-fluorescence or that PFA fixation quenches the fluorescence of GFP-**VP22**. We further considered whether elution of **VP22** from methanol-fixed cells and postfixation binding to surrounding cells contributed to the increased detection of spread observed after methanol fixation. The results show that while this could occur, it appeared to be a minor effect not accounting for the observed **VP22** cell-to-cell spread in culture.

14/3,AB/3 (Item 3 from file: 155)
DIALOG(R) File 155:MEDLINE(R)

10275147 99273417 PMID: 10341871

Intercellular delivery of thymidine kinase prodrug activating enzyme by the herpes simplex virus protein, VP22.

Dilber M S; Phelan A ; Aints A; Mohamed A J; Elliott G; Smith C I; O'Hare P

Department of Medicine, Huddinge Hospital, Karolinska Institute, Sweden.

Gene therapy (ENGLAND) Jan 1999, 6 (1) p12-21, ISSN 0969-7128
Journal Code: 9421525

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

We demonstrate that fusion proteins consisting of the **herpes simplex virus (HSV) transport protein VP22** linked in frame to HSV thymidine kinase (tk) retain the ability to be transported between cells. In vivo radiolabelling experiments and in vitro assays show that the fusion proteins also retain tk activity. When transfected COS cells, acting as a source of the **VP22** -tk chimera, were co-plated on to gap junction-negative neuroblastoma cells, ganciclovir treatment induced efficient cell death in the recipient neuroblastoma cell monolayer. No such effect was observed with COS cells transfected with tk alone. Tumours established in mice with neuroblastoma cell lines expressing **VP22** -tk regressed upon administration of ganciclovir. Furthermore tumours established from 50:50 mixtures of **VP22** -tk transduced and nontransduced cells also regressed while no significant effect was observed in similar experiments with cells transduced with tk alone. **VP22** mediated transport may thus have application in a clinical setting to amplify delivery of the target protein in enzyme-prodrug protocols.

14/3,AB/4 (Item 4 from file: 155)

09848652 98254727 PMID: 9592391

Intercellular delivery of functional p53 by the herpesvirus protein VP22 .

Phelan A ; Elliott G; O'Hare P

Marie Curie Research Institute, Surrey, UK.

Nature biotechnology (UNITED STATES) May 1998, 16 (5) p440-3, ISSN 1087-0156 Journal Code: 9604648

Comment in Nat Biotechnol. 1998 May;16(5) 418-20; Comment in PMID 9592386

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

The **herpes** simplex virus type 1 (HSV-1) virion protein **VP22** exhibits the remarkable property of intercellular trafficking whereby the protein spreads from the cell in which it is synthesized to many surrounding cells. In addition to having implications for protein trafficking mechanisms, this function of **VP22** might be exploited to overcome a major hurdle in gene therapy, i.e., efficient delivery of genes and gene products. We show that chimeric polypeptides, consisting of **VP22** linked to the entire p53 protein, retain their ability to spread between cells and accumulate in recipient cell nuclei. Furthermore the p53- **VP22** chimeric protein efficiently induces apoptosis in p53 negative human osteosarcoma cells resulting in a widespread cytotoxic effect. The intercellular delivery of functional p53- **VP22** fusion protein is likely to prove beneficial in therapeutic strategies based on restoration of p53 function. These results, demonstrating intracellular transport of large functional proteins, indicate that **VP22** delivery may have applications in gene therapy.

14/3,AB/5 (Item 1 from file: 34)

DIALOG(R) File 34:SciSearch(R) Cited Ref Sci

(c) 2002 Inst for Sci Info. All rts. reserv.

08421220 Genuine Article#: 283RT Number of References: 43

Title: Cytoplasm-to-nucleus translocation of a herpesvirus tegument protein during cell division (ABSTRACT AVAILABLE)

Author(s): Elliott G (REPRINT) ; OHare P

Corporate Source: MARIE CURIE RES INST,VIRUS ASSEMBLY GRP/SURREY RH8

OTL//ENGLAND/ (REPRINT); MARIE CURIE RES INST,HERPESVIRUS GRP/SURREY

RH8 OTL//ENGLAND/

Journal: JOURNAL OF VIROLOGY, 2000, V74, N5 (MAR), P2131-2141

ISSN: 0022-538X Publication date: 20000300

Publisher: AMER SOC MICROBIOLOGY, 1325 MASSACHUSETTS AVENUE, NW, WASHINGTON, DC 20005-4171

Language: English Document Type: ARTICLE

Abstract: We have previously shown that the **herpes** simplex virus tegument protein **VP22** localizes predominantly to the cytoplasm of expressing cells. We have also shown that **VP22** has the unusual property of intercellular spread, which involves the movement of **VP22** from the cytoplasm of these expressing cells into the nuclei of nonexpressing cells. Thus, **VP22** can localize in two distinct subcellular patterns. By utilizing time-lapse confocal microscopy of live cells expressing a green fluorescent protein-tagged protein, we now report in detail the intracellular trafficking properties of **VP22** in expressing cells, as opposed to the intercellular trafficking of **VP22** between expressing and nonexpressing cells. Our results show that during interphase **VP22** appears to be targeted exclusively to the cytoplasm of the expressing cell. However, at the early stages of mitosis **VP22** translocates from the cytoplasm to the nucleus, where it immediately binds to the condensing cellular chromatin and remains bound there through all stages of mitosis and chromatin decondensation into the G(1) stage of the next cycle. Hence, in **VP22** -expressing cells the subcellular localization of the protein is regulated by the cell cycle such that initially cytoplasmic protein becomes nuclear

during cell division, resulting in a gradual increase over time in the number of nuclear **VP22**-expressing cells. Importantly, we demonstrate that this process is a feature not only of **VP22** expressed in isolation but also of **VP22** expressed during virus infection. Thus, **VP22** utilizes an unusual pathway for nuclear targeting in cells expressing the protein which differs from the nuclear targeting pathway used during intercellular trafficking.

14/3,AB/7 (Item 3 from file: 34)

DIALOG(R) File 34:SciSearch(R) Cited Ref Sci
(c) 2002 Inst for Sci Info. All rts. reserv.

07593888 Genuine Article#: 185ZG Number of References: 32

Title: Live-cell analysis of a green fluorescent protein-tagged herpes simplex virus infection (ABSTRACT AVAILABLE)

Author(s): Elliott G (REPRINT) ; OHare P

Corporate Source: MARIE CURIE RES INST,/SURREY RH1 0TL//ENGLAND/ (REPRINT)

Journal: JOURNAL OF VIROLOGY, 1999, V73, N5 (MAY), P4110-4119

ISSN: 0022-538X Publication date: 19990500

Publisher: AMER SOC MICROBIOLOGY, 1325 MASSACHUSETTS AVENUE, NW,
WASHINGTON, DC 20005-4171

Language: English Document Type: ARTICLE

Abstract: Many stages of the **herpes** simplex virus maturation pathway have not yet been defined. In particular, little is known about the assembly of the virion tegument compartment and its subsequent incorporation into maturing virus particles. Here we describe the construction of a **herpes** simplex virus type 1 (HSV-1) recombinant in which we have replaced the gene encoding a major tegument protein, **VP22**, with a gene expressing a green fluorescent protein (GFP)-**VP22** fusion protein (GFP-22). We show that this virus has growth properties identical to those of the parental virus and that newly synthesized GFP-22 is detectable in live cells as early as 3 h postinfection. Moreover, we show that GFP-22 is incorporated into the HSV-1 virion as efficiently as **VP22**, resulting in particles which are visible by fluorescence microscopy. Consequently, we have used time lapse confocal microscopy to monitor GFP-22 in live-cell infection, and we present time lapse animations of GFP-22 localization throughout the virus life cycle. These animations demonstrate that GFP-22 is present in a diffuse cytoplasmic location when it is initially expressed but evolves into particulate material which travels through an exclusively cytoplasmic pathway to the cell periphery. In this way, we have for the first time visualized the trafficking of a **herpesvirus** structural component within live, infected cells.

14/3,AB/8 (Item 4 from file: 34)

DIALOG(R) File 34:SciSearch(R) Cited Ref Sci
(c) 2002 Inst for Sci Info. All rts. reserv.

07390562 Genuine Article#: 159JQ Number of References: 4

Title: Intercellular trafficking of VP22 -GFP fusion proteins (ABSTRACT AVAILABLE)

Author(s): Elliott G; OHare P (REPRINT)

Corporate Source: MARIE CURIE RES INST,CHART/SURREY RH8 0TL//ENGLAND/
(REPRINT); MARIE CURIE RES INST,/SURREY RH8 0TL//ENGLAND/

Journal: GENE THERAPY, 1999, V6, N1 (JAN), P149-151

ISSN: 0969-7128 Publication date: 19990100

Publisher: STOCKTON PRESS, HOUNDMILLS, BASINGSTOKE RG21 6XS, HAMPSHIRE,
ENGLAND

Language: English Document Type: ARTICLE

Abstract: The **herpes** simplex virus protein **VP22** exhibits the unusual property of intercellular transport whereby after being synthesised in a subpopulation of cells, in which it is largely cytoplasmic, the protein is transported to adjacent cells where it accumulates mainly in the nucleus. Here we examine the transport of a fusion protein

consisting of **VP22** linked to the green fluorescent protein (GFP). Intercellular transport, nuclear accumulation and chromatin binding of **VP22** -GFP could be detected by intrinsic GFP fluorescence in fixed cells. However, while the cytoplasmic localisation of **VP22** -GFP could be detected in live cells actively synthesising the protein, we were unable to detect intercellular transport by intrinsic GFP fluorescence in live cells, indicating that the levels of transported protein may be below those required for live detection, or that GFP fluorescence was quenched. The use of antibody to GFP was more sensitive than intrinsic GFP fluorescence and allowed ready detection of transport and nuclear accumulation of **VP22** -GFP. Intercellular transport was also confirmed in coplating experiments. Consistent with previous results showing a requirement for the C-terminus of **VP22** in transport of the native protein, a fusion protein consisting of GFP linked to the N-terminal 1-192 residues of **VP22** failed to transport between cells. The results support the proposal that **VP22** has the ability to transport cargo proteins between cells and that it has significant potential in the field of gene therapy.

14/3,AB/9 (Item 5 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
(c) 2002 Inst for Sci Info. All rts. reserv.

06888467 Genuine Article#: ZZ446 Number of References: 44
Title: Herpes simplex virus type 1 tegument protein **VP22** induces the stabilization and hyperacetylation of microtubules (ABSTRACT AVAILABLE)

Author(s): Elliott G (REPRINT) ; OHare P
Corporate Source: MARIE CURIE RES INST,THE CHART/SURREY RH8 OTL//ENGLAND/
(REPRINT)

Journal: JOURNAL OF VIROLOGY, 1998, V72, N8 (AUG), P6448-6455
ISSN: 0022-538X Publication date: 19980800
Publisher: AMER SOC MICROBIOLOGY, 1325 MASSACHUSETTS AVENUE, NW,
WASHINGTON, DC 20005-4171

Language: English Document Type: ARTICLE

Abstract: The role of the **herpes** simplex virus type 1 tegument protein **VP22** during infection is as yet undefined. We have previously shown that **VP22** has the unusual property of efficient intercellular transport, such that the protein spreads from single expressing cells into large numbers of surrounding cells. We also noted that in cells expressing **VP22** by transient transfection, the protein localizes in a distinctive cytoplasmic filamentous pattern. Here we show that this pattern represents a colocalization between **VP22** and cellular microtubules. Moreover, we show that **VP22** reorganizes microtubules into thick bundles which are easily distinguishable from nonbundled microtubules. These bundles are highly resistant to microtubule-depolymerizing agents such as nocodazole and incubation at 4 degrees C, suggesting that **VP22** has the capacity to stabilize the microtubule network. In addition, we show that the microtubules contained in these bundles are modified by acetylation, a marker for microtubule stability. Analysis of infected cells by both immunofluorescence and measurement of microtubule acetylation further showed that colocalization between **VP22** and microtubules, and induction of microtubule acetylation, also occurs during infection. Taken together, these results suggest that **VP22** exhibits the properties of a classical microtubule-associated protein (MAP) during both transfection and infection. This is the first demonstration of a MAP encoded by an animal virus.

14/3,AB/10 (Item 6 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
(c) 2002 Inst for Sci Info. All rts. reserv.

05534503 Genuine Article#: WE970 Number of References: 35

Title: Intercellular trafficking and protein delivery by a herpesvirus structural protein (ABSTRACT AVAILABLE)

Author(s): Elliott G (REPRINT) ; OHare P

Corporate Source: MARIE CURIE RES INST, THE CHART/OXTED RH8
OTL/SURREY/ENGLAND/ (REPRINT)

Journal: CELL, 1997, V88, N2 (JAN 24), P223-233

ISSN: 0092-8674 Publication date: 19970124

Publisher: CELL PRESS, 1050 MASSACHUSETTES AVE, CIRCULATION DEPT,
CAMBRIDGE, MA 02138

Language: English Document Type: ARTICLE

Abstract: We show that the HSV-1 structural protein **VP22** has the remarkable property of intercellular transport, which is so efficient that following expression in a subpopulation the protein spreads to every cell in a monolayer, where it concentrates in the nucleus and binds chromatin. **VP22** movement was observed both after delivery of DNA by transfection or microinjection and during virus infection. Moreover, we demonstrate that **VP22** trafficking occurs via a nonclassical Golgi-independent mechanism. Sensitivity to cytochalasin D treatment suggests that **VP22** utilizes a novel trafficking pathway that involves the actin cytoskeleton. In addition, we demonstrate intercellular transport of a **VP22** fusion protein after endogenous synthesis or exogenous application, indicating that **VP22** may have potential in the field of protein delivery.

14/3,AB/13 (Item 1 from file: 357)

DIALOG(R) File 357: Derwent Biotech Res.

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0260679 DBA Accession No.: 2001-00255 PATENT

Aggregated composition suitable for phototherapy or prophylaxis of psoriasis, eczema or skin cancer and for delivering nucleic acids and proteins into cells, comprises transport protein VP22 and an oligonucleotide - plasmid-mediated gene transfer, expression in Escherichia coli, antisense oligonucleotide, ribozyme and recombinant protein aggregate for cancer therapy

AUTHOR: O'Hare P F J; Normand N M

CORPORATE SOURCE: Cambridge, UK.

PATENT ASSIGNEE: Phogen 2000

PATENT NUMBER: WO 200053722 PATENT DATE: 20000914 WPI ACCESSION NO.:
2000-594314 (2056)

PRIORITY APPLIC. NO.: GB 9930499 APPLIC. DATE: 19991224

NATIONAL APPLIC. NO.: WO 2000GB897 APPLIC. DATE: 20000310

LANGUAGE: English

ABSTRACT: An aggregated composition (I) containing a protein having the transport function of a transport protein **VP22**, and an oligonucleotide (antisense or ribozyme) or DNA, is claimed. Also claimed are: making (I) by: mixing a protein with the transport function of **VP22** with the oligonucleotide or DNA; and allowing the obtained mixture to form aggregates of 0.1-5 microns; and a cell preparation which has been treated with (I). (I) is useful for preparing a medicament for therapy and for delivering molecules to cells in vitro. The medicament is suitable for phototherapy. The aggregates are delivered to target cells such as tumor cells in vivo using e.g. liposome and are useful for treating psoriasis, eczema or skin cancer. In an example, a protein designated 159-301 protein consisting of amino acids 159-301 of the herpes-simplex virus-2 **VP22** protein along with a his6 tag at the C-terminus and a 20-mer phosphorothioate oligonucleotide labeled at the 3'-end with fluorescein was prepared. 159-301 was made in an Escherichia coli expression system expressing a plasmid encoding 159-301 protein. The aggregates were then added to HeLa cells and incubated for 12 hr at 37 deg. (28pp)

14/3,AB/14 (Item 2 from file: 357)

DIALOG(R) File 357: Derwent Biotech Res.

0227200 DBA Accession No.: 98-08797

Intercellular delivery of functional p53 by the herpes virus protein

VP22 - fusion protein gene expression in e.g. COS-1 cell culture and potential application to gene therapy

AUTHOR: Phelan A ; Elliott G; +O'Hare P

CORPORATE AFFILIATE: Marie-Curie-Res.Inst.Oxted

CORPORATE SOURCE: Marie Curie Research Institute, The Chart, Oxted, Surrey, RH8 OTL, UK. email:p.o'hare@mcri.ac.uk

JOURNAL: Nat.Biotechnol. (16, 5, 440-43) 1998

ISSN: 1087-0156 CODEN: NABIF

LANGUAGE: English

ABSTRACT: The **herpes** simplex virus type-1 (HSV-1) virion protein **VP22** exhibits intercellular trafficking activity, whereby the protein spreads from the cell in which it is synthesized to many surrounding cells. As well as having implications for protein trafficking mechanisms, this activity of **VP22** may be used to overcome a major hurdle in gene therapy, e.g. efficient delivery of genes and gene products. Chimeric proteins comprising **VP22** linked to the entire p53 protein were constructed and showed to retain their ability to spread between cells and accumulate in recipient cell nuclei. The p53- **VP22** chimeric protein efficiently induced apoptosis in p53 negative human osteosarcoma cells resulting in a widespread cytotoxic effect. The intercellular delivery of functional p53- **VP22** fusion protein is likely to prove beneficial in the therapeutic strategies based on restoration of p53 function. These results show intracellular transport of large active proteins and show that **VP22** delivery may be applicable to gene therapy. (18 ref)

?

24/3,AB/1 (Item 1 from file: 155)
DIALOG(R) File 155:MEDLINE(R)

10275155 99273415 PMID: 10341869

Catch VP22 : the hitch-hiker's ride to gene therapy?

Murphy A L; Murphy S J

Gene therapy (ENGLAND) Jan 1999, 6 (1) p4-5, ISSN 0969-7128

Journal Code: 9421525

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

24/3,AB/5 (Item 1 from file: 65)

DIALOG(R) File 65:Inside Conferences

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02626245 INSIDE CONFERENCE ITEM ID: CN027353851

Intercellular Delivery of Functional p53 by the Herpesvirus Protein VP22

O'Hare, P.

CONFERENCE: New cancer strategies-Annual conference; 3rd

P: 9:05

Newton Upper Falls, MA, Cambridge Healthtech Institute, (1998)

LANGUAGE: English DOCUMENT TYPE: Conference Selected preprinted abstracts and programme

CONFERENCE SPONSOR: Cambridge Healthtech Institute

CONFERENCE LOCATION: Washington, DC

CONFERENCE DATE: Sep 1998 (199809) (199809)

24/3,AB/7 (Item 1 from file: 266)

DIALOG(R) File 266:FEDRIP

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00329867

IDENTIFYING NO.: 1R01GM60986-01A1 AGENCY CODE: CRISP

VP22 **TRAFFICKING FOR MAXIMAL GENE THERAPY**

PRINCIPAL INVESTIGATOR: SPLITTER, GARY A

ADDRESS: UNIVERSITY OF WISCONSIN 1655 LINDEN DRIVE MADISON, WI 53706-1581

PERFORMING ORG.: UNIVERSITY OF WISCONSIN MADISON, MADISON, WISCONSIN

SPONSORING ORG.: NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES

FY : 2001

SUMMARY: DESCRIPTION (Copied from Applicant Abstract): Gene therapy is a highly promising strategy for a wide variety of biomedical applications including **cancer** treatment, immunization and gene restoration. **VP22** possesses novel trafficking ability where protein produced in one expressing cell, traffics to the nuclei of neighboring non-expressing cells. Further, **VP22** chimerics can carry large, effector proteins without altering the function of the attached proteins. In addition to trafficking, **VP22** has novel intracellular localization properties including microtubule association and nuclear targeting. Although most **VP22** data have been obtained from studies with **herpes** simplex virus (HSV-1), we have found bovine **herpesvirus** -1 (BHV-1) **VP22** to have improved biotherapeutic potential compared to HSV- **VP22** . Importantly, BHV- 1 **VP22** can traffic a fused effector protein up to 20 times more efficiently than HSV-1. BHV- and HSV- **VP22** possess only 28.7 percent amino acid homology with numerous motif differences suggesting the opportunity for considerable diversity in structure and function. Our long-term goal is to maximize **VP22** -mediated gene therapy by defining **VP22** intercellular transport mechanisms as well as in vivo repercussions regarding **VP22** biotherapeutic delivery. To accomplish our long-range goal, we have plasmids expressing **VP22** of BHV-1 as well as defined **VP22** mutants and will elucidate the mechanisms of **VP22** that contribute to gene delivery by achieving the following Objectives:

1. We will functionally map the regions of **VP22** that govern trafficking and localization.

(a) We will engineer truncations of **VP22** to evaluate regions responsible for trafficking and nuclear localization. We will build on our data that the carboxy-terminal half of **VP22** is essential for trafficking.

(b) We will assess the effects of **VP22** mutants (tyrosine residues that are phosphorylated and two important cysteines in **VP22**) on trafficking and nuclear localization.

(c) We will utilize a novel cross-linking agent and MALDI-mass spectrometry to identify the specific interaction of **VP22** with nuclear and cytoplasmic proteins.

2. We will develop and analyze **VP22** delivery of thymidine kinase to tumors for suicide gene therapy.

(a) We will evaluate the efficiency of **VP22** delivery using a suicide gene therapy approach, where fusion genes will be constructed encoding **VP22**-tk chimeric polypeptides. This construct will be compared to vector-tk only by testing in vitro.

(b) We will also evaluate the efficacy of **VP22**-tk chimeric polypeptides in vivo **tumor** killing in the presence of ganciclovir.

24/3,AB/8 (Item 2 from file: 266)

DIALOG(R) File 266:FEDRIP

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00303857

IDENTIFYING NO.: 5P01CA66726-06 0002 AGENCY CODE: CRISP

VECTOR DEVELOPMENT /PRECLINICAL TESTING

PRINCIPAL INVESTIGATOR: ALBELDA, STEVEN M

ADDRESS: UNIVERSITY OF PENNSYLVANIA 3600 SPRUCE STREET PHILADELPHIA, PA 19104-4283

PERFORMING ORG.: UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA, PENNSYLVANIA

SPONSORING ORG.: NATIONAL **CANCER** INSTITUTE

FY : 2001

SUMMARY: DESCRIPTION: (Applicant's Description) The short term goals of this project are to develop new strategies to augment HSVtk therapy and to test these new systems in well characterized animal models of mesothelioma. The long term goals are to move the most promising of these new approaches into phase I clinical trials for mesothelioma.

The first specific aim will be to develop and evaluate adenoviruses containing "improved" versions of HSV/k. Two hypotheses will be tested: (1) mutant versions of HSVtk with increased affinity and/or improved kinetics will augment **tumor** killing efficacy and (2) a chimeric HSVtk/**VP22** fusion protein will augment **tumor** killing efficacy due to the ability of the **VP22** protein (a tegument protein produced by **Herpes Simplex Virus**) to transfer from transduced to non-transduced cells. Accordingly, Ad vectors containing mutant HSVtk's with augmented ability to phosphorylate ganciclovir and containing a chimeric transgene consisting of HSVtk coupled to the HSV-**VP22** protein will be produced and tested. The second specific aim will be to develop and evaluate replication-competent adenoviral vectors expressing HSVtk. Two hypotheses will be tested: (1) use of replicating vectors (even if only 1 or 2 rounds of replication occur) will be able to deliver transgene to a larger number of **tumor** cells and thus enhance efficacy and (2) adenoviral vectors in which a **tumor**-associated promoter regulates EIA expression will confer replication selectivity in the appropriate **tumor** cells. A fully replicative virus containing the HSVtk gene inserted into the E3 region will be produced and studied. In addition, Ad mutants that replicate selectively in tumors will be constructed and tested. This will be accomplished by disrupting the normal Ad EIA promoter region and inserting **tumor**-selective promoters into this region. The third Specific Aim will be to evaluate the use of specific cytokines to augment HSVtk/GCV efficacy. The hypothesis that immune augmentation can increase the efficacy of HSVt/dGCV gene therapy will be tested. Intracavitary Ad. HSVtk therapy will be combined with intracavitary injection of specific cytokines that are commercially available and have

August 27, 2002

been shown to have some efficacy in mesothelioma (IL-2, Interferon-cq and interferon-7). In addition, investigators from this Project will work closely with investigat from this Project to provide the animals models needed for their pharmacokineti and imaging studies.

24/3,AB/9 (Item 1 from file: 315)
DIALOG(R)File 315:ChemEng & Biotec Abs
(c) 2002 DECHEMA. All rts. reserv.

463750 CEABA Accession No.: 30-08-013212 DOCUMENT TYPE: Journal
Title: Phogen's herpes protein technology boosts anticancer gene therapy.
CORPORATE SOURCE: Phogen Cambridge UK Karolinska Inst. Stockholm Sweden
JOURNAL: Pharmaceutical Business News, Volume: 15, Issue: 334, Page(s):
26

ISSN: 09560661
PUBLICATION DATE: 22 Jan 1999 (19990122) LANGUAGE: English
ABSTRACT: Phogen has developed a gene construct comprising the thymidine kinase (tk) gene linked to the gene for the **herpes** simplex virus protein **VP22**. When the construct was administered to **tumour** cells, the cells expressed the **VP22** -tk fusion protein, which was absorbed into surrounding **tumour** cells. The fusion protein kept its tk activity, this increasing the number of **tumour** cells killed on subsequent ganciclovir administration. The improved efficacy has also been demonstrated in animal models.

24/3,AB/10 (Item 2 from file: 315)
DIALOG(R)File 315:ChemEng & Biotec Abs
(c) 2002 DECHEMA. All rts. reserv.

450256 CEABA Accession No.: 29-12-022431 DOCUMENT TYPE: Journal
Title: Cancer gene therapy: guardian gene restored.
AUTHOR: Newell, J.
CORPORATE SOURCE: UK
JOURNAL: Chem. Br., Volume: 34, Issue: 8, Page(s): 19
CODEN: CHMBAY ISSN: 00093106
PUBLICATION DATE: Aug 1998 (980800) LANGUAGE: English
ABSTRACT: Researchers at the Marie Curie Research Institute, Oxted, Surrey, have developed a means for restoring p53, the most important **cancer** -protecting guardian gene, into **cancer** cells which have lost their own p53. The effect of restoring the lost genes will be to make malignant cells destroy themselves. The researchers have linked the p53 protein to protein **VP 22** produced by **Herpes** simplex virus. **VP22** can spread very rapidly from cells infected by the virus to other cells where it accumulates in the nuclei. The hybrid protein enters and induces apoptosis in human osteosarcoma cells in culture as effectively as p53 alone.

24/3,AB/11 (Item 3 from file: 315)
DIALOG(R)File 315:ChemEng & Biotec Abs
(c) 2002 DECHEMA. All rts. reserv.

416054 CEABA Accession No.: 28-06-013336 DOCUMENT TYPE: Journal
Title: Phogen to focus on herpes drug delivery.
CORPORATE SOURCE: Phogen Cambridge UK Cantab Pharmaceuticals plc London UK Marie Curie Cancer Care
JOURNAL: Biotechnol. Newswatch, , Page(s): 14
ISSN: 02753685
PUBLICATION DATE: 3 Mar 1997 (970303) LANGUAGE: English
ABSTRACT: Phogen, a new biotech company formed by Canatab Pharmaceuticals and Marie Curie **Cancer** Care, will focus on the development of drug delivery systems using **VP22 herpes** virus protein technology. The company will study **VP22** for the delivery of enzymes, hormones, transcription factors and metabolic inhibitors against **cancer**, as

well as the delivery of DNA for tumour -specific antigens or nucleic acids.

24/3,AB/13 (Item 2 from file: 357)
DIALOG(R) File 357:Derwent Biotech Res.
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0229623 DBA Accession No.: 98-11220 PATENT
Use of the microtubule binding function and transport properties of herpes virus VP22 protein - to study and manipulate mammal cell structure, growth, division and death in vitro and in vivo

AUTHOR: Elliot G D

CORPORATE SOURCE: Cambridge, UK.

PATENT ASSIGNEE: Phogen 1998

PATENT NUMBER: WO 9842742 PATENT DATE: 981001 WPI ACCESSION NO.:
98-531948 (9845)

PRIORITY APPLIC. NO.: GB 975903 APPLIC. DATE: 970321

NATIONAL APPLIC. NO.: WO 98GB873 APPLIC. DATE: 980323

LANGUAGE: English

ABSTRACT: The use of **herpes virus VP22** protein or derivative with microtubule (MT) binding function to stabilize animal cellular MT is claimed. Also claimed is the use of **herpes virus VP22** or variants with **VP22** homology and MT binding function to: retard or arrest growth and cell division or induce cell death in an animal cell; deliver MT binding drugs; deliver a substance to cell MT; study the cell cycle, particularly cell division; retard or arrest cell division of **neoplastic** cells in vitro or in vivo; and to inhibit cell proliferation of a protozoal parasite in vivo or in vitro. Products in which taxol is coupled with **VP22** can be infused to ovary **cancer** patients. Compared to current anti- **cancer** therapies, treatments based upon **VP22** can be administered in a variety of ways. **VP22** and derivatives can increase the effects of ionizing radiation and enhance the activity of MT binding substances (e.g. taxol), thus reducing the dose required and also the associated severe side effects. Also **VP22** can protect a proportion of cells from depolymerizing agents (e.g. nocodazole) whilst diseased cells are treated. Preferably, **VP22** is coupled to an **VP22** antibody recombinantly. (16pp)

24/3,AB/15 (Item 4 from file: 357)
DIALOG(R) File 357:Derwent Biotech Res.
(c) 2002 Thomson Derwent & ISI. All rts. reserv.

0227093 DBA Accession No.: 98-08690
Ferrying proteins to the other side - membrane translocating protein fusion protein for potential use in gene therapy or as recombinant vaccine

AUTHOR: Fernandez T; Bayley H

CORPORATE AFFILIATE: Univ.Texas-A+M

CORPORATE SOURCE: Department of Medical Biochemistry and Genetics, Texas A+M Health Science Center, College Station, TX 77843, USA.
email: bayley@tamu.edu

JOURNAL: Nat.Biotechnol. (16, 5, 418-20) 1998

ISSN: 1087-0156 CODEN: NABIF

LANGUAGE: English

ABSTRACT: Approaches to ferry proteins across the plasma membrane of a cell may be useful in gene therapy and to introduce proteins into cells. A membrane translocating sequence of 12 amino acids from the hydrophobic region of the signal peptide of Kaposi fibroblast growth factor was fused to proteins upto 41 kDa and used to enhance uptake into mammal cells. **Herpes simplex virus-1 protein VP22** ferried proteins between cells, a property shared by HIV virus-1 Tat. **VP22** may be useful for gene therapy by allowing the transport of p53 into **cancer** cells and thereby induce apoptotic cell death. The ferry proteins may find a role in gene-directed enzyme prodrug therapy. A double bystander effect may occur if an enzyme were delivered to target cells as cargo encoded by a

virus. The enzyme would spread from an infected cell, and prodrug molecules activated in the expanded volume of affected tissue would diffuse. There may be safety concerns with such powerful gene therapy agents, but purified ferry proteins could attack **tumor** cells or act as vaccines. The proteins may also be used to deliver oligonucleotides or cytotoxic drugs. (18 ref)

24/3,AB/16 (Item 1 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)
(c) 2002 AMERICAN CHEMICAL SOCIETY. All rts. reserv.

131347510 CA: 131(26)347510k PATENT
Gene therapy vectors utilizing recombination and their use in antitumor therapy
INVENTOR(AUTHOR): Margison, Geoffrey Paul; Marples, Brian; Scott, Simon; Hendry, Jolyon Hindson
LOCATION: UK,
ASSIGNEE: Cancer Research Campaign Technology Limited
PATENT: PCT International ; WO 9960142 A2 DATE: 19991125
APPLICATION: WO 99GB1362 (19990517) *GB 9810423 (19980515)
PAGES: 89 pp. CODEN: PIXXD2 LANGUAGE: English CLASS: C12N-015/85A; A61K-048/00B; C12N-015/52B; C12N-015/53B; C12N-009/00B; C12N-009/02B
DESIGNATED COUNTRIES: AE; AL; AM; AT; AU; AZ; BA; BB; BG; BR; BY; CA; CH; CN; CU; CZ; DE; DK; EE; ES; FI; GB; GD; GE; GH; GM; HR; HU; ID; IL; IN; IS; JP; KE; KG; KP; KR; KZ; LC; LK; LR; LS; LT; LU; LV; MD; MG; MK; MN; MW; MX; NO; NZ; PL; PT; RO; RU; SD; SE; SG; SI; SK; SL; TJ; TM; TR; TT; UA; UG; US; UZ; VN; YU; ZA; ZW; AM; AZ; BY; KG; KZ; MD; RU; TJ; TM
DESIGNATED REGIONAL: GH; GM; KE; LS; MW; SD; SL; SZ; UG; ZW; AT; BE; CH; CY; DE; DK; ES; FI; FR; GB; GR; IE; IT; LU; MC; NL; PT; SE; BF; BJ; CF; CG; CI; CM; GA; GN; GW; ML; MR; NE; SN; TD; TG

24/3,AB/19 (Item 2 from file: 349)
DIALOG(R)File 349:PCT FULLTEXT
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00528790
GENE THERAPY VECTORS AND THEIR USE IN ANTITUMOUR THERAPY
VECTEURS DE THERAPIE GENIQUE ET UTILISATION DE CES DERNIERS DANS UNE THERAPIE ANTITUMORALE

Patent Applicant/Assignee:

CANCER RESEARCH CAMPAIGN TECHNOLOGY LIMITED,
MARGISON Geoffrey Paul,
MARPLES Brian,
SCOTT Simon,
HENDRY Jolyon Hindson

Inventor(s):

MARGISON Geoffrey Paul,
MARPLES Brian,
SCOTT Simon,
HENDRY Jolyon Hindson,

Patent and Priority Information (Country, Number, Date):

Patent: WO 9960142 A2 19991125
Application: WO 99GB1362 19990517 (PCT/WO GB9901362)
Priority Application: GB 9810423 19980515

Designated States: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZA ZW GH GM KE LS MW SD SL SZ UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM GA GN GW ML MR NE SN TD TG

Publication Language: English
Fulltext Word Count: 19481

English Abstract

Vector material useful for antitumour therapy contains: (a) a tumour cell sensitizing gene or genes of which expression in a tumour cell yields a sensitizing gene expression product having a potential to cause tumour cells to be killed and destroyed, or to be eliminated, or otherwise to be inactivated, or to be rendered sensitive and/or vulnerable to destruction; (b) a sensitizing gene promoter; (c) at least one control gene; and (d) a control gene expression regulatory system responsive in use in a transfected cell to the effect of a predetermined exogenous or endogenous expression inducing influence, e.g. ionizing radiation, heat or a chemical inducing agent, so as to induce expression of the control gene to yield an expression product having a capacity to establish an operative linkage between the sensitizing gene promoter and the sensitizing gene or genes effective to trigger and switch on or permit continuous or permanent expression of the latter to bring about continuous production of the sensitizing gene expression product. This is preferably achieved by arranging for the control gene to encode a recombinase enzyme that acts on recombinase target sites in a Cre-loxP or Flp-frt site specific recombination system to remove an expression preventing stop cassette sequence between the sensitizing gene(s) and the promoter for the latter. In some embodiments the tumour sensitizing gene expression product will be an enzyme or other bioactive agent that can activate an inactive prodrug.

French Abstract

L'invention concerne un vecteur presentant une grande utilite pour une therapie antitumorale. Ce vecteur comprend (a) un gene de sensibilisation aux cellules tumorales ou des genes dont l'expression dans une cellule tumorale produit un produit d'expression de gene de sensibilisation presentant le potentiel de tuer et de detruire ou d'eliminer les cellules tumorales, ou encore d'inactiver ces dernieres ou de les rendre sensibles et/ou vulnérables a la destruction; (b) un promoteur de gene de sensibilisation; (c) au moins un gene regulateur; et (d) un systeme de regulation de l'expression du gene regulateur agissant lors de son utilisation dans une cellule transfectee en reponse a une expression endogene ou exogene predeterminee induisant, par exemple, un rayonnement ionisant, un effet thermique ou un agent inducteur chimique, de maniere a induire l'expression du gene regulateur pour produire un produit d'expression pouvant etabli une liaison operationnelle entre le promoteur de gene de sensibilisation et le gene de sensibilisation ou les genes capables de declencher ou de permettre l'expression permanente ou continue de ces derniers pour declencher la production continue du produit d'expression du gene de sensibilisation. Cela est assure, de preference, en permettant au gene regulateur de coder une recombinase, enzyme qui agit sur des sites cibles de la recombinase dans un systeme de recombinaison cible pour le Flp-frt ou Cre-loxP pour retirer une sequence d'arret de l'expression entre le gene ou les genes de sensibilisation et le promoteur de ce dernier. Dans certains modes de realisation, le produit d'expression du gene de sensibilisation aux tumeurs peut etre une enzyme ou un autre agent biologique actif qui permet d'activer un medicament inactif.

24/3,AB/21 (Item 4 from file: 349)

DIALOG(R) File 349:PCT FULLTEXT

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00513775

ENHANCED PRODRUG ACTIVATION

ACTIVATION AMELIOREE DE PROMEDICAMENTS

Patent Applicant/Assignee:

OXFORD BIOMEDICA (UK) LIMITED,

STRATFORD Ian James,

PATTERSON Adam Vorn,

KINGSMAN Susan Mary,

KAN On,

GRIFFITHS Leigh,

August 27, 2002

MITROPHANOUS Kyriacos,

Inventor(s):

STRATFORD Ian James,

PATTERSON Adam Vorn,

KINGSMAN Susan Mary,

KAN On,

GRIFFITHS Leigh,

MITROPHANOUS Kyriacos,

Patent and Priority Information (Country, Number, Date):

Patent: WO 9945127 A2 19990910

Application: WO 99GB674 19990305 (PCT/WO GB9900674)

Priority Application: GB 984841 19980306; GB 9818103 19980819; GB 992081 19990129

Designated States: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES

FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU

LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA

UG US UZ VN YU ZW GH GM KE LS MW SD SL SZ UG ZW AM AZ BY KG KZ MD RU TJ

TM AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE BF BJ CF CG CI

CM GA GN GW ML MR NE SN TD TG

Publication Language: English

Fulltext Word Count: 45240

English Abstract

A prodrug activating agent comprising: a) a localisation domain and b) a prodrug activation domain for activating a prodrug in a target cell.

French Abstract

L'invention concerne un agent d'activation de promedicaments renfermant:

a) un domaine de localisation et b) un domaine d'activation de

promedicaments destine a activer un promedicament dans une cellule cible.

24/3,AB/26 (Item 9 from file: 349)

DIALOG(R)File 349:PCT FULLTEXT

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00475188

INHIBITORS OF CELL-CYCLE PROGRESSION AND USES RELATED THERETO

INHIBITEUR DE LA PROGRESSION DU CYCLE CELLULAIRE ET UTILISATIONS ASSOCIEES

Patent Applicant/Assignee:

MITOTIX INC,

GYURIS Jeno,

LAMPHERE Lou,

BEACH David H,

Inventor(s):

GYURIS Jeno,

LAMPHERE Lou,

BEACH David H,

Patent and Priority Information (Country, Number, Date):

Patent: WO 9906540 A2 19990211

Application: WO 98US15759 19980729 (PCT/WO US9815759)

Priority Application: US 97902572 19970729

Designated States: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES

FI GB GE GH GM HR HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD

MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US

UZ VN YU ZW GH GM KE LS MW SD SZ UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE

CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM GA GN

GW ML MR NE SN TD TG

Publication Language: English

Fulltext Word Count: 25845

English Abstract

The present invention pertains to novel inhibitors of cyclin-dependent kinases (CDKs), particularly CDK/cyclin complexes, which inhibitors can be used to control proliferation and/or differentiation of cells in which the inhibitors are introduced.

August 27, 2002

French Abstract

L'invention concerne de nouveau inhibiteurs de kinases dependantes des cyclines (CDK), et en particulier de complexes CDK/cycline. Ces inhibiteurs peuvent etre utilises pour reguler la proliferation et/ou la differenciation des cellules dans lesquelles ils sont introduits.

24/3,AB/27 (Item 10 from file: 349)

DIALOG(R) File 349:PCT FULLTEXT

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00464680

HERPES **SIMPLEX VIRUS** VP22 **VACCINES AND METHODS OF USE**
VACCINS AU VP22 CONTRE LE VIRUS DE L' HERPES SIMPLEX ET PROCEDE
D'UTILISATION DE CES VACCINS

Patent Applicant/Assignee:

CHIRON CORPORATION,

Inventor(s):

BURKE Rae Lyn,

TIGGES Michael A,

Patent and Priority Information (Country, Number, Date):

Patent: WO 9855145 A1 19981210

Application: WO 98US10664 19980526 (PCT/WO US9810664)

Priority Application: US 9747359 19970602

Designated States: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES

FI GB GE GH GM GW HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD

MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG UZ

VN YU ZW GH GM KE LS MW SD SZ UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH

CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM GA GN ML

MR NE SN TD TG

Publication Language: English

Fulltext Word Count: 20281

English Abstract

Vaccines containing **herpes simplex virus (HSV) VP22** polypeptides capable of eliciting a cellular immune reponse and methods for treating and preventing HSV infections using the vaccines are disclosed. The vaccines can include additional HSV polypeptides, such as HSV glycoproteins. Also disclosed are methods of DNA immunization.

French Abstract

Cette invention concerne des vaccins qui contiennent des polypeptides **VP22** du virus de l' **herpes simplex (VHS)** permettant d'eliciter une reponse immune cellulaire. Cette invention concerne egalement des procedes de traitement et de prevention d'infections par le VHS qui font appel a ces vaccins. Ces vaccins peuvent egalement comprendre des polypeptides complementaires de VHS, tels que des glycoproteines de VHS. Cette invention concerne enfin des procedes d'immunisation au niveau de l'ADN.

24/3,AB/31 (Item 14 from file: 349)

DIALOG(R) File 349:PCT FULLTEXT

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00452278

VP22 **PROTEINS AND USES THEREOF**
PROTEINES VP22 ET LEURS UTILISATIONS

Patent Applicant/Assignee:

PHOGEN LIMITED,

ELLIOTT Gillian Daphne,

Inventor(s):

ELLIOTT Gillian Daphne,

Patent and Priority Information (Country, Number, Date):

Patent: WO 9842742 A1 19981001

Application: WO 98GB873 19980323 (PCT/WO GB9800073)

Priority Application: GB 975903 19970321

Designated States: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES
FI GB GE GH GM GW HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD
MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US
UZ VN YU ZW GH GM KE LS MW SD SZ UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE
CH DE DK ES FI FR GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM GA GN ML
MR NE SN TD TG

Publication Language: English

Fulltext Word Count: 6412

English Abstract

Herpesviral VP22 proteins (and variants) are used to modify cell structure and cell division, by their newly found property of binding to microtubules in cells. Uses of **VP22** to exploit this property include stabilisation of animal cellular microtubules in vivo and in vitro, e.g. to retard or arrest cell division or induce cell death. The microtubule binding function of **VP22** can be exploited by reagent use in vitro to study microtubules or the cell cycle particularly at cell division, and pharmaceutically to retard or arrest cell division of cells such as **neoplastic** cells or protozoal parasite cells in vitro or in vivo.

French Abstract

On utilise des proteines **VP22** du virus herpetique (ou leurs variants) pour modifier une structure cellulaire ou une division cellulaire, en raison de leur propriete, recemment decouverte, de liaison aux microtubules dans des cellules. Une utilisation de la **VP22** pour exploiter cette propriete consiste a stabiliser in vivo ou in vitro des microtubules cellulaires d'animaux (c'est-a-dire a retarder ou arreter la division cellulaire, ou a provoquer la degenerescence cellulaire). La fonction de liaison de la **VP22** aux microtubules peut etre exploitee par l'utilisation d'un reactif in vitro pour etudier les microtubules ou le cycle cellulaire, particulierement au niveau de la division cellulaire; elle peut egalement etre exploitee pharmaceutiquement pour retarder ou arreter in vivo ou in vitro la division de cellules telles que les cellules **neoplastiques** ou les cellules parasites protozoaires.

24/3,AB/33 (Item 16 from file: 349)

DIALOG(R) File 349:PCT FULLTEXT

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00442402

FUSION PROTEINS FOR INTRACELLULAR AND INTERCELLULAR TRANSPORT AND THEIR USES

PROTEINES HYBRIDES PERMETTANT LE TRANSPORT INTRACELLULAIRE ET INTERCELLULAIRE ET UTILISATIONS DE CES PROTEINES

Patent Applicant/Assignee:

MARIE CURIE **CANCER** CARE,
O'HARE Peter Francis Joseph,
ELLIOTT Gillian Daphne

Inventor(s):

O'HARE Peter Francis Joseph,
ELLIOTT Gillian Daphne,

Patent and Priority Information (Country, Number, Date):

Patent: WO 9832866 A1 19980730

Application: WO 98GB207 19980123 (PCT/WO GB9800207)

Priority Application: GB 971363 19970123; GB 9716398 19970801

Designated States: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES
FI GB GE GH GM GW HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD
MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US
UZ VN YU ZW GH GM KE LS MW SD SZ UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE
CH DE DK ES FI FR GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM GA GN ML
MR NE SN TD TG

Publication Language: English

Fulltext Word Count: 10144

August 27, 2002

English Abstract

Coupled polypeptides and fusion polypeptides for intracellular transport, and their preparation and use, include (i) an aminoacid sequence with the transport function of **herpesviral VP22** protein (or homologue, e.g. from VZV, BHV or MDV) and (ii) another protein sequence selected from (a) proteins for cell cycle control; (b) suicide proteins; (c) antigenic sequences or antigenic proteins from microbial and viral antigens and **tumour** antigens; (d) immunomodulating proteins; and (e) therapeutic proteins. The coupled proteins can be used for intracellular delivery of protein sequences (ii), to exert the corresponding effector function in the target cell, and the fusion polypeptides can be expressed from corresponding polynucleotides, vectors and host cells.

French Abstract

La presente invention concerne des polypeptides couples et des polypeptides hybrides permettant le transport intracellulaire, ainsi que leur preparation et leur utilisation. Lesdits polypeptides contiennent (i) une sequence d'acides amines dotee de la fonction de transport de la proteine du virus de l' **herpes VP22** (ou d'un homologue provenant par exemple du virus varicelle-zona, du virus- **herpes** bovin ou du virus MDV) et (ii) une autre sequence de proteine selectionnee a partir de (a) proteines permettant la regulation du cycle cellulaire; (b) de proteines suicide; (c) de sequences antigeniques ou de proteines antigeniques provenant d'antigenes microbiens et viraux et d'antigenes tumoraux; (d) de proteines immunomodulatrices; et (e) de proteines therapeutiques. On peut utiliser les proteines couplees pour l'administration intracellulaire de sequences de proteines (ii), pour exercer la fonction effectrice correspondante dans la cellule cible, et on peut exprimer les polypeptides hybrides a partir des polynucleotides, vecteurs et cellules hotes correspondants.

24/3,AB/36 (Item 19 from file: 349)
DIALOG(R) File 349:PCT FULLTEXT
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00364939

TRANSPORT PROTEINS AND THEIR USES PROTEINES DE TRANSPORT ET LEUR UTILISATION

Patent Applicant/Assignee:

O'HARE Peter Francis Joseph,
ELLIOTT Gillian Daphne,

Inventor(s):

O'HARE Peter Francis Joseph,
ELLIOTT Gillian Daphne,

Patent and Priority Information (Country, Number, Date):

Patent: WO 9705265 A1 19970213

Application: WO 96GB1831 19960725 (PCT/WO GB9601831)

Priority Application: GB 9515568 19950728; GB 961570 19960126

Designated States: AL AM AT AU AZ BB BG BR BY CA CH CN CU CZ DE DK EE ES FI
GB GE HU IL IS JP KE KG KP KR KZ LK LR LS LT LU LV MD MG MK MN MW MX NO
NZ PL PT RO RU SD SE SG SI SK TJ TM TR TT UA UG US UZ VN KE LS MW SD SZ
UG AM AZ BY KG KZ MD RU TJ TM AT BE CH DE DK ES FI FR GB GR IE IT LU MC
NL PT SE BF BJ CF CG CI CM GA GN ML MR NE SN TD TG

Publication Language: English

Fulltext Word Count: 8591

English Abstract

The present invention relates to transport proteins, in particular **VP22** and homologues thereof, and to methods of delivering these proteins and any associated molecules to a target population of cells. This transport protein has applications in gene therapy and methods of targeting agents to cells where targeting at high efficiency is required.

French Abstract

La presente invention concerne des proteines de transport, notamment la proteine **VP22** et des homologues de celle-ci, ainsi que des procedes

d'apport de ces proteines et de toute molecule associee a une population cible de cellules. On peut utiliser cette proteine de transport dans la therapie genique, ainsi que dans des procedes de ciblage, par des agents, de cellules dans lesquelles un ciblage hautement efficace est requis.

?

39/3,AB/37 (Item 37 from file: 155)
DIALOG(R) File 155:MEDLINE(R)

06850179 91175391 PMID: 1706611

Distribution of multi - drug resistance -associated P-glycoprotein in normal and neoplastic human tissues. Analysis with 3 monoclonal antibodies recognizing different epitopes of the P-glycoprotein molecule.

van der Valk P; van Kalken C K; Ketelaars H; Broxterman H J; Scheffer G; Kuiper C M; Tsuruo T; Lankelma J; Meijer C J; Pinedo H M; et al

Department of Pathology, Free University Hospital, Amsterdam, The Netherlands.

Annals of oncology : official journal of the European Society for Medical Oncology / ESMO (NETHERLANDS) 1990, 1 (1) p56-64, ISSN 0923-7534

Journal Code: 9007735

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

P-glycoprotein is a molecule strongly associated with **multi - drug resistance** to certain cytostatic drugs, including adriamycin, vincristine, and daunorubicin. Using 3 monoclonal antibodies directed at different epitopes of this molecule (JSB-1, MRK16, C219) we investigated the tissue distribution of P-glycoprotein in normal and malignant human tissues, employing a routine immunoperoxidase technique. P-glycoprotein was found in the gastrointestinal epithelium, epithelia of the bronchi, mammary gland, pancreatic ducts, renal tubules, prostate gland, salivary gland, sweat glands of the skin, as well as in bile canaliculi and ductules, the adrenal and in endothelium of capillaries in various organs, most notably the brain. Mostly the pattern of reactivity of the 3 antibodies was similar, but some distinctly different staining reactions were seen. Reactivity was found in a variety of human tumors, arising from tissues normally expressing P-glycoprotein. Knowledge of the distribution and function of this molecule in both normal and malignant tissues may predict resistance and thus may influence choice of therapy. The role of P-glycoprotein in normal tissues and its implications for chemotherapy is discussed.

39/3,AB/39 (Item 39 from file: 155)
DIALOG(R) File 155:MEDLINE(R)

06593129 90294369 PMID: 1694250

Multi - drug resistance of a doxorubicin-resistant bladder cancer cell line.

Floyd J W; Lin C W; Prout G R

Urology Research Laboratory, Massachusetts General Hospital, Boston 02114.

Journal of urology (UNITED STATES) Jul 1990, 144 (1) p169-71, ISSN 0022-5347 Journal Code: 0376374

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

A bladder **tumor** cell line resistant to doxorubicin (MGH-U1R) has been established previously by culturing a human transitional cell carcinoma cell line (MGH-U1) in increasing concentrations of the drug. MGH-U1R is 40 times more resistant to doxorubicin than MGH-U1. In the present study, MGH-U1R was evaluated for its **multi - drug resistance** or pleiotropism by testing against other chemotherapeutic agents. MGH-U1R was found to be 188 times more resistant to vinblastine and 13 times more resistant to etoposide than MGH-U1, while remained sensitive to bleomycin. Taken together with earlier evidence that the resistance of MGH-U1R to doxorubicin can be reversed by a calcium-channel blocker verapamil, and the measured over-expression of the mdrl gene in these cells, MGH-U1R has the characteristic multiple drug resistance properties similar to other

established doxorubicin resistant carcinoma cell lines. H-U1R may be a useful model for the development of strategies in overcoming drug-resistance in the treatment of transitional cell carcinoma.

39/3,AB/40 (Item 40 from file: 155)
DIALOG(R) File 155:MEDLINE(R)

06547197 90243379 PMID: 2335394

Reversal of multi - drug resistance in human KB cell lines by structural analogs of verapamil.

Pirker R; Keilhauer G; Raschack M; Lechner C; Ludwig H
First Medical Clinic, Vienna, Austria.

International journal of cancer. Journal international du cancer (UNITED STATES) May 15 1990, 45 (5) p916-9, ISSN 0020-7136 Journal Code: 0042124

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Several structural analogs of verapamil were studied for their ability to reverse **multi - drug resistance** (MDR) in human KB cell lines. D595, D792 and verapamil completely reversed resistance to colchicine and adriamycin. D595 and D792 had a higher reversing potency than verapamil. Devapamil, gallopamil, emopamil and D528 partially reversed MDR. The reversing potency of a drug did not correlate with its calcium antagonistic activity. No differences in reversing potency between (R)-isomers, (L)-isomers and the racemic forms were observed in the case of both verapamil and emopamil. (R)-verapamil, which has less calcium antagonistic activity and less in vivo toxicity than racemic verapamil, and D792, which has higher reversing potency and less in vivo toxicity than racemic verapamil, should be suitable for clinical applications to overcome drug resistance in **cancer** patients.

39/3,AB/41 (Item 41 from file: 155)
DIALOG(R) File 155:MEDLINE(R)

06308200 90001068 PMID: 2477051

Flow cytometric analysis of Hoechst 33342 uptake as an indicator of multi - drug resistance in human lung cancer .

Morgan S A; Watson J V; Twentyman P R; Smith P J

Clinical Oncology and Radiotherapeutics Unit, Addenbrooke's Hospital, Cambridge, UK.

British journal of cancer (ENGLAND) Sep 1989, 60 (3) p282-7, ISSN 0007-0920 Journal Code: 0370635

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Cytotoxic drug resistance developing after chemotherapy is thought to be the main cause of treatment failure in several human tumours, including small cell lung **cancer** (SCLC). Cell lines showing drug resistance following prolonged exposure to a single agent frequently acquire resistance to several functionally unrelated drugs, the phenomenon of **multi - drug resistance** (MDR). Classical MDR is thought to arise from changes effecting a reduction in intracellular availability of cytotoxic drugs. We describe a flow cytometry (FCM) technique to monitor the MDR phenotype in drug resistant variants of SCLC and non-SCLC cell lines. The technique is based on a multiparametric analysis of the nuclear binding of a model chemotherapeutic agent, the fluorescent dye Hoechst 33342 (Ho342), which is capable of supra-vital staining of DNA in intact, viable cells. A laboratory derived drug resistant SCLC cell line, H69/LX4, showed a significant (30%) reduction in nuclear binding compared to the parental line H69/P. Exposure to verapamil (VPL) rapidly increased (within 2 min) nuclear binding of Ho342, and the new equilibrium of nuclear staining,

attained within 20 min, remained lower than the level achieved in the parental cell line, suggesting some ability of H69/LX4 to limit the effect of the drug efflux blocker. A drug resistant large cell carcinoma line showed only a small reduction (10%) in nuclear binding when compared to the parent line, and this difference was not altered by VPL. A drug resistant adenocarcinoma line showed less than 10% difference in nuclear binding compared with the parental line and neither line was significantly affected by VPL treatment. Our findings suggest that different mechanisms of resistance may occur in lung tumours of different tissue types. This technique may be extended to the rapid and direct examination of biopsy specimens of human solid tumours for evidence of **multi - drug resistance**

39/3,AB/42 (Item 42 from file: 155)
DIALOG(R) File 155:MEDLINE(R)

05893168 88330240 PMID: 2458323

Monoclonal antibody JSB-1 detects a highly conserved epitope on the P-glycoprotein associated with multi - drug - resistance .

Scheper R J; Bulte J W; Brakkee J G; Quak J J; van der Schoot E; Balm A J ; Meijer C J; Broxterman H J; Kuiper C M; Lankelma J; et al
Department of Pathology, Free University Hospital, Amsterdam, The Netherlands.

International journal of cancer. Journal international du cancer (UNITED STATES) Sep 15 1988, 42 (3) p389-94, ISSN 0020-7136 Journal Code: 0042124

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Resistance to multiple chemotherapeutic agents is a common clinical problem in the treatment of **cancer** . This resistance may occur before primary therapy or be acquired during treatment. We have generated a monoclonal antibody (MAb) (JSB-I), specific for a conserved epitope on the plasma membrane 170- to 180-kDa glycoprotein, the expression of which is strongly correlated with the degree of **multi - drug resistance** (MDR). JSB-I strongly binds to both Chinese-hamster-derived MDR cell lines and human MDR cell lines, including cell lines derived from lung and ovary. A drug-sensitive revertant line, and the corresponding drug-sensitive parent lines, showed only weak reactivity or none at all. JSB-I reacts strongly to air-dried or acetone-fixed cells and therefore has potential value for diagnostic detection of MDR cells in human **tumor** samples.

39/3,AB/43 (Item 43 from file: 155)
DIALOG(R) File 155:MEDLINE(R)

04939091 86012923 PMID: 3900592

An antigen related to the phenotype of multi - drug resistance can be induced in vivo and used as a target for immunotherapy of rat leukemia.

Brox A; Price G; Sullivan A K

Leukemia research (ENGLAND) 1985, 9 (8) p987-92, ISSN 0145-2126

Journal Code: 7706787

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Several laboratories have reported that new plasma membrane peptides appear in rodent and human cells after induction of in-vitro resistance to vinca alkaloids, anthracyclines and other anti- **neoplastic** drugs. Recently, murine monoclonal antibodies have been produced that recognize surface components of such drug-resistant cells. The work presented here describes the development of an in-vivo animal model of this phenomenon using a rat myeloid leukemia. Brown Norway rats were made leukemic with promyelocytes of the BNML line and subsequently were treated with 7.7 mg

kg-1 of daunorubicin. After eight cycles of passage-treatment-regrowth, the resulting cells reacted with this antibody in immunofluorescence and cytotoxicity assays. Animals injected with cells that had been pre-incubated with antibody in the absence of complement survived significantly longer than did the controls. Further prolongation of survival occurred when the cells were treated with a second antibody of a different specificity. These results demonstrate that some of the changes associated with in-vitro drug resistance occur also in vivo and potentially may be exploited as a focus for immunotherapy.

39/3,AB/44 (Item 44 from file: 155)
DIALOG(R) File 155:MEDLINE(R)

04535301 84219773 PMID: 6728022

Amplification of specific DNA sequences correlates with multi - drug resistance in Chinese hamster cells.

Roninson I B; Abelson H T; Housman D E; Howell N; Varshavsky A

Nature (ENGLAND) Jun 14-20 1984, 309 (5969) p626-8, ISSN 0028-0836
Journal Code: 0410462

Contract/Grant No.: CA17575; CA; NCI; CA18662; CA; NCI; CA33297; CA; NCI;

+

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Mammalian cells selected for resistance to certain cytotoxic drugs frequently develop cross-resistance to a broad spectrum of other drugs unrelated in structure to the original selective agent. This phenomenon constitutes a major problem in **cancer** chemotherapy. **Multi - drug resistance** arises from decreased intracellular drug accumulation, apparently due to an alteration of the plasma membrane. The observation of double minute chromosomes or homogeneously staining regions in some of the multi-drug-resistant cell lines suggests that gene amplification underlies this phenomenon. We have used the technique of DNA renaturation in agarose gels to detect, compare and clone amplified DNA sequences in Adriamycin- and colchicine-resistant sublines of Chinese hamster cells. We show that both Adriamycin- and colchicine-resistant cells contain amplified DNA fragments, some of which are amplified in both of these independently derived cell lines. Furthermore, loss of the **multi - drug resistance** phenotype on growth in the absence of drugs correlates with the loss of amplified DNA. These results strongly suggest that the DNA sequences which are amplified in common in multi-drug-resistant cell lines include the gene(s) responsible for a common mechanism of **multi - drug resistance** in these cells. We have cloned one of the commonly amplified DNA fragments and show that the degree of amplification of this fragment in the cells correlates with the degree of their drug resistance.

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43/3,AB/7 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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11505344 BIOSIS NO.: 199800286676

Hyperplastic/dysplastic pathways in aberrant crypt foci (ACF) from human colon.

AUTHOR: Nascimbeni R(a); Villanacci V; Donato F; Salerni B(a)
AUTHOR ADDRESS: (a)Dep. Surg., Univ. Brescia, Brescia**Italy
JOURNAL: Gastroenterology 114 (4 PART 2):pA653 April 15, 1998
CONFERENCE/MEETING: Digestive Disease Week and the 99th Annual Meeting of the American Gastroenterological Association New Orleans, Louisiana, USA May 16-22, 1998
SPONSOR: American Gastroenterological Association
ISSN: 0016-5085
RECORD TYPE: Citation
LANGUAGE: English
1998

43/3,AB/8 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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11505121 BIOSIS NO.: 199800286453

Azoxymethane (AOM)-induced aberrant crypt foci (ACF) and colorectal tumors in F344 rats.

AUTHOR: Ghirardi M(a); Villanacci V; Nascimbeni R(a); Fontana M G(a); Mariani P P(a); Di Betta E(a); Salerni B(a)
AUTHOR ADDRESS: (a)Dep. Surg., Univ. Brescia, Brescia**Italy
JOURNAL: Gastroenterology 114 (4 PART 2):pA600 April 15, 1998
CONFERENCE/MEETING: Digestive Disease Week and the 99th Annual Meeting of the American Gastroenterological Association New Orleans, Louisiana, USA May 16-22, 1998
SPONSOR: American Gastroenterological Association
ISSN: 0016-5085
RECORD TYPE: Citation
LANGUAGE: English
1998

43/3,AB/9 (Item 3 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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11373569 BIOSIS NO.: 199800154901

Are aberrant crypt foci (ACF) markers of neoplastic change during colorectal carcinogenesis?

AUTHOR: Park Hyun Sook(a); Goodlad Robert A; Wright Nicholas A
AUTHOR ADDRESS: (a)Dep. Histopathol., Imperial Coll. Sch. Med. At Hammersmith Hosp., London**UK
JOURNAL: Journal of Pathology 184 (SUPPL.):p2A 1998
CONFERENCE/MEETING: 176th Meeting of the Pathological Society of Great Britain and Ireland London, England, UK January 7-9, 1998
SPONSOR: Departments of Histopathology and Medical Microbiology, Imperial College School of Medicine at Chari
ISSN: 0022-3417
RECORD TYPE: Citation
LANGUAGE: English
1998

43/3,AB/10 (Item 4 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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10957477 BIOSIS NO.: 1997-578622

Aberrant crypt foci (ACF) in neoplastic and non- neoplastic human colon.

AUTHOR: Nascimbeni R; Salerni B; Fontana M G; Mittempergher F; Ghiradi M

AUTHOR ADDRESS: Dep. Surgery, Univ. Brescia, Brescia**Italy

JOURNAL: Gastroenterology 112 (4 SUPPL.):pA625 1997

CONFERENCE/MEETING: Digestive Disease Week and the 97th Annual Meeting of the American Gastroenterological Association Washington, D.C., USA May 11-14, 1997

ISSN: 0016-5085

RECORD TYPE: Citation

LANGUAGE: English

1997

43/3,AB/18 (Item 1 from file: 94)

DIALOG(R)File 94:JICST-EPlus

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04043712 JICST ACCESSION NUMBER: 99A0237918 FILE SEGMENT: JICST-E

Effects of Nonsteroidal anti-inflammatory drugs on ACF .

TAKAYAMA TETSUJI (1); KATSUKI SHIN'ICHI (1); NOBUOKA JUN (1); OI MASAO (1); MIYANISHI KOJI (1); SASAKI NORIYUKI (1); NIITSU YOUSHIRO (1)

(1) Sapporo Med. Coll.

Shokaki Gan no Hassei to Shinten(Journal of Japanese Research Society for Gastroenterological Carcinogenesis), 1998, VOL.10, PAGE.129-131, FIG.1, TBL.2, REF.11

JOURNAL NUMBER: L2665AAE ISSN NO: 0915-4817

UNIVERSAL DECIMAL CLASSIFICATION: 616-006-085 616.3-006 615.276.03

LANGUAGE: Japanese COUNTRY OF PUBLICATION: Japan

DOCUMENT TYPE: Journal

ARTICLE TYPE: Original paper

MEDIA TYPE: Printed Publication

43/3,AB/23 (Item 1 from file: 266)

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MOLECULAR CHARACTERIZATION OF ACF (ABERRANT CRYPT FOCI) PROGRESSION

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PERFORMING ORG.: UNIVERSITY OF CONNECTICUT SCH OF MED/DNT, FARMINGTON, CONNECTICUT

SPONSORING ORG.: NATIONAL CANCER INSTITUTE

FY : 2001

SUMMARY: Aberrant crypt foci (ACF) is a precursor for colon cancer . Human and mouse ACF are either hyperplastic or dysplastic, a classification that is based on morphology and their potential to form tumors. Understanding mechanisms that govern formation of ACFs and their conversion to fully malignant colonic lesions is the focus of this proposal. It is known that heritable characteristics of inbred mice lead to either susceptibility or resistance to formation of colon tumors after carcinogen treatment. We will test two hypotheses that attempt to define genetic mechanisms that determine differential susceptibility . Specific aim 1: Does malignant potential of ACFs, formed in mice of differing colon tumor susceptibilities, result from the specific complement of gene mutations that target cells acquire? Using the colon carcinogen, azoxymethane, we will generate populations of ACF in mice. We have shown that hyperplastic ACF are produced in resistant strains, but fail to progress in carcinomas. We will conduct a detailed morphometric and genetic analysis of sub-populations of ACFs that will enable us to understand why azoxymethane-induced lesions fail to progress

to tumors in resistant AKR mice. Laser capture micro-dissection will be used to isolate DNA from single crypts for mutational analyses of tumor related genes. 1.1 What is the time course of azoxymethane-induced ACF formation in tumor susceptible and resistant mice? 1.2 What functional characteristics distinguish hyperplastic and dysplastic ACF? 1.3 Are there differences between hyperplastic and dysplastic ACFs in the frequency of mutations in K-ras, APC, beta-catenin and p53? Specific aim 2: Is malignant potential of ACFs controlled by expression of, and signalling by, the secretory phospholipase A2, encoded by the Mpl locus? Among genetic factors that affect tumorigenesis factors that affect tumorigenesis in the multiple intestinal neoplasia (Min) model is the gene product of Mpl, a calcium-dependent non-pancreatic secretory phospholipase (Pla2g2a [Pla2]). sPla2 plays a role in inflammation and hydrolyzes the sn-2 position of glycerolipids, releasing arachidonic acid for prostaglandin synthesis. We present evidence that sPla2 is differentially expressed in mouse clones in a pattern inversely correlated with tumor susceptibility to azoxymethane: A/J < SWR < AKR. This suggests that colonic sPla2 also plays a role in chemically-induced tumorigenesis equivalent to its role in the Min model. We propose to explore the mechanism by which sPla2 affects tumor formation in sensitive and resistant mice. 2.1 What colon cell types produce sPla2/ Are there changes in sPla2 levels or function within and adjacent to carcinogen-induced ACF and tumors? 2.2 Can AKR resistances to carcinogen be reversed with the use of specific inhibitors of sPla2? 2.3 Can over-expression of sPla2 in transgenic A/J mice protect against azoxymethane-induced tumorigenesis?

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